Application of monodentate secondary phosphine oxides, a new class of chiral ligands, in Ir(I)-catalyzed asymmetric imine hydrogenation

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Monodentate Secondary Phosphine Oxides, a New Class of Chiral Ligands. Their Application in Ir (I)-Catalyzed Asymmetric Imine Hydrogenation.

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Ligand Syntheses

Ligand **1** was prepared according to a literature procedure[1]. The ligands **2-7** were prepared in a similar manner, modified to the extent that the Grignard reagent was added to the solution of the $RPCl_2$ (reverse addition).

***iso*-propylphosphinoyl-benzene (2)**[2]

Colorless oil, isolated yield 36%. ^{31}P ($CDCl_3$, 75MHz) δ 39.38 (s) ^{1}H($CDCl_3$, 300MHz) δ 1.08 (dd, 3H, CH_3, J=7.33, 9.15Hz), 1.14 (dd, 3H, CH_3, J=7.32, 9.16Hz), 2.03-2.21 (m, 1H), 7.22 (dd, 1H, P-H, J=2.2, 458.28 Hz), 7.3-7.74 (m, 5H) ^{13}C($CDCl_3$, 121MHz) δ 129.81, 127.71, 127.56, 126.50 (d, J =94Hz), 126.12, 125.96, 25.70 (d, J = 69.59Hz), 12.34, 11.76 HRMS (EI^+) M^+ for $C_9H_{13}OP$, 168.07264, calcd. 168.07040

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-hexane /Ethanol=92.5/7.5, t_1 =15.1min, $[\ ]_D^{21}$ = -14.4° (C=0.25, $CHCl_3$), t_2 = 17.3min, $[\ ]_D^{21}$ = +11.2° (C=0.285, $CHCl_3$)

***2-tert*-butylphosphinoyl-naphthalene (3)**

White powder, isolated yield 14%. ^{31}P ($CDCl_3$, 75MHz) δ 47.03 (s) ^{1}H($CDCl_3$, 300MHz) δ 1.18 (d, 9H, $3CH_3$, J=16.6Hz), 7.17 (d, 1H, P-H, J_{P-H} = 453.89Hz), 7.55-7.70 (m, 4H), 7.86-7.96 (m, 3H), 8.24 (d, 1H, J=14.41Hz) ^{13}C($CDCl_3$, 121MHz) δ 133.54 (d, J=12.56Hz), 131.37, 130.65, 127.17, 126.72, 126.40, 125.54, 124.23, 124.02, 123.51, 30.72 (d, J = 69.05Hz), 21.96 HRMS (EI^+) M^+ for $C_{14}H_{17}OP$ 232.10117, calcd. 232.10170

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-hexane/ethanol = 67/33, t_1 = 5.61min, mp 129-131°C, $[\ ]_D^{21}$= -38.8°(C=0.245, $CHCl_3$), t_2 = 7.91min, mp 138-140°C, $[\ ]_D^{21}$ = +38.5° (C=0.275, $CHCl_3$)

2-methoxy-*tert*-butylphosphinoyl-benzene (4)

Colorless oil, isolated yield 68%. ^{31}P ($CDCl_3$, 75MHz) δ 35.58 (s) ^{1}H($CDCl_3$, 300MHz) δ 1.15 (d, 9H, $3CH_3$, J=17.09Hz), 3.83 (s, 3H, OCH_3), 6.86-6.93 (m, 1H), 7.01-7.08 (m, 1H), 7.36 (d, 1H, P-H, J_{P-H}= 484.4Hz), 7.43-7.51(m, 1H), 7.63-7.73 (m, 1H) ^{13}C($CDCl_3$, 121MHz) δ 159.35(d, J= 4.19 Hz), 132.42, 131.90, 119.14, 116.61, 109.05, 53.71, 30.92 (d, J=70.96Hz), 22.06 HRMS (EI^+) M^+ for $C_{11}H_{17}O_2P$ 212.09790, calcd. 212.09661

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-hexane/ethanol=67/33, t_1 =3.99min, [ ]$_D^{21}$= -15.1^o (C=0.35, $CHCl_3$), t_2 = 5.88min, [ ]$_D^{21}$ = +11.8^o (C=0.365, $CHCl_3$).

(3,5-dimethyl)-*tert*-butylphosphinoyl-benzene (5)

White solid, isolated yield 65%. ^{31}P ($CDCl_3$, 75MHz) δ 47.76 (s) ^{1}H($CDCl_3$, 300MHz) δ 1.13 (d, 9H, 3CH_3, J=16.6Hz), 2.35 (s, 6H, 2CH_3), 6.95 (d, 1H, P-H, J_{P-H} = 452.42Hz), 7.17(s, 1H, CH), 7.28(s, 1H, CH), 7.22(s, 1H, CH) ^{13}C ($CDCl_3$, 121MHz) δ 136.65 (d, J =12.59 Hz), 132.77, 127.30, 127.00, 126.79, 125.49, 30.24(d, J=69.05Hz), 21.87, 21.84, 19.62 HRMS (EI$^+$) M^+ for $C_{12}H_{19}OP$ 210.11830, calcd. 210.11735

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-hexane /Ethanol=92.5/7.5, t_1 =7.23min, mp 144-147^{o}C, [ ]$_D^{21}$ = +9.4^o (C=0.265, $CHCl_3$), t_2 = 17.3min, mp 126-128^{o}C, [ ]$_D^{21}$ = -9.8^o (C=0.275, $CHCl_3$).

(2,4,6-trimethyl)-*tert*-butylphosphinoyl-benzene (6)

Colorless oil, isolated yield 21% over 2 steps. ^{31}P ($CDCl_3$, 75MHz) δ 38.16 (s) ^{1}H($CDCl_3$, 300MHz) δ 1.16 (d, 9H, 3CH_3, J_{P-H} = 16.6Hz), 2.22 (s, 3H, CH_3), 2.49 (br, 6H, 2CH_3), 6.83 (br, 2H, 2CH), 7.55 (d, 1H, P-H, J_{P-H} = 455.59Hz) ^{13}C($CDCl_3$, 121MHz) δ 139.81, 139.77, 128.67, 128.12, 120.23 (d, J=88.12Hz), 32.70 (d, J= 69.05Hz), 22.78, 22.72, 20.45, 20.35, 19.12 HRMS (EI$^+$) M^+ for $C_{13}H_{21}OP$ 224.13412, calcd. 224.13299

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml /min, RT, UV 254nm, n-Heptane/2-propanol=95/5, t_1=8.971min, mp 109.5-112^{o}C, [ ]$_D^{21}$ = -16.9^o (C=0.255, $CHCl_3$), t_2=13.728min, mp 105-107^{o}C, [ ]$_D^{21}$ = +20.4^o (C=0.275, $CHCl_3$).

2-phenylphosphinoyl-naphthalene (7)

White solid, isolated yield 35%. ^{31}P ($CDCl_3$, 75MHz) δ 21.38 (s) ^{1}H($CDCl_3$, 300MHz) δ 6.85-7.00 (m, 5H), 7.01-7.35 (m, 6H), 7.72 (d, 1H, P-H, J_{P-H} = 483.18Hz), 7.90 (d, 1H, J=15.63Hz) ^{13}C($CDCl_3$, 121MHz) δ 133.07 (d, J=2.29Hz), 130.92, 130.71, 130.43, 128.91, 128.68, 127.74, 127.19, 126.94, 126.88, 126.57, 126.12, 125.73, 125.33, 123.309, 123.07 HRMS (EI$^+$) M^+ for $C_{16}H_{13}OP$ 252.06907, calcd.252.07039

The enantiomerically pure ligands were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-Hexane/2-propanol=56/44, t_1=22.4min, mp 73-75^{o}C, [ ]$_D^{21}$= -5.2^o (C=0.27, $CHCl_3$), t_2=26.859 min, mp 81-83^{o}C, [ ]$_D^{21}$ = +6.0^o(C=0.25, $CHCl_3$) (lit. [3] mp184-186^{o}C, No independent measure of optical purity was given in this paper. In view of the low rotation reported the material must have had very low optical purity., [ ]$_D$ = -0.59^o,C=0.476, $CHCl_3$).

(*1R, 7R*)-9,9-Dimethyl-4-hydrido-4-oxo-2, 2, 6, 6-tetraphenyl-3, 5, 8, 10-tetraoxa-4-phosphabicyclo [5.3.0] decane (8)[4]

In a 100ml Schlenk vessel, was placed (4*R,* 5*R*)-4,5-bis-(hydroxy-diphenylmethyl)-[1,3] dioxolane)(*R,R*-Taddol) (2mmol, 0.94g) and 5ml dry toluene. The solution was cooled down to –78^{o}C, and PCl_3 (3.0mmol, 0.26ml) was added over 20mins. The solution was

allowed to come to RT and stirring was continued for 3h. After cooling down to 0°C, 5ml H_2O was added slowly. After warming up to RT stirring was continued for 30mins. The mixture was extracted with CH_2Cl_2 (3x10 ml), with brine (3x) and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (SiO_2, EtOAc/Hexane=1/1) to obtain a white powder; isolated yield 75%. Mp 224-226°C (dec.), $[\ ]_D^{21}$ =-268.4° (C=0.275, $CHCl_3$), (lit. [4] mp 226-227°C, dec., $[\ ]_D$ = -289.9 °, C=1.56, $CHCl_3$), ^{31}P ($CDCl_3$, 75MHz) δ -4.73, -4.79 (we presume the double peak is due to the presence of two slowly interconverting conformers) ^{1}H($CDCl_3$, 300MHz) δ 0.56 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 5.21 (d, 1H, CH, J=7.82Hz), 5.36 (d, 1H, CH, J=8.06Hz), 7.08 (d, 1H, P-H, J_{P-H} =726.85Hz), 7.23-7.46 (m, 16H), 7.56-7.63 (m, 4H) ^{13}C($CDCl_3$,121MHz) δ 142.16 (d, J=2.68Hz), 141.65 (d, J=2.25Hz), 137.66 (d, J=8.78Hz), 137.45 (d, J=6.48Hz), 127.31, 127.22, 127.00, 126.83, 126.70, 126.51, 126.40, 126.04, 125.86, 125.38, 125.30, 112.90, 87.31, 87.14, 78.57, 78.30, 25.28, 24.79 MS(CI^+,%) 530($M+NH_4^+$,100).

2, 5-diphenyl-phospholane-1-oxide (9)
This ligand was prepared according to a literature method[5].
The pure enantiomers were obtained by preparative HPLC, chiralpak AD column, Preparative 250x20 mm ID flow 20 ml/min, RT, UV 254nm, n-heptane/isopropanol=75/25, t_1=10.486min, t_2=13.071min.

Imines

Imines were prepared from the ketones and the amines by azeotropic reflux in toluene using molecular sieves 4Å. All imines are known compounds[6] with the exception of **13**.

(4-chlorophenyl)-*N*-[(*E*)-1-phenylethylidene]methanamine (13)
Isolated yield 44%, yellow oil, ^{1}H ($CDCl_3$, 300MHz) major isomer: δ 2.28 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.20-7.39 (m, 6H), 7.79-7.82 (m, 2H), 7.91 (d, 1H, J=7.32Hz) minor: δ 2.33, 4.88, ^{13}C($CDCl_3$, 121MHz) major isomer: δ 165.53, 137.98, 130.78, 127.76, 127.29, 127.09, 126.91 125.40, 53.48, 16.83 minor: 164.69, 139.41, 127.83, 126.43, 124.45, 54.74, 14.44. In the ^{1}H NMR and the ^{13}C NMR some resonances of the minor isomer are obscured. HRMS (EI^+) $C_{15}H_{14}NCl$ 243.08030, calcd. 243.08147

Typical procedure for imine hydrogenation

In a 5ml glass vial provided with a magnetic stirrer, a mixture of $[Ir(COD)Cl]_2$ (3.4mg, 0.005mmol), SPO ligand (0.02 mmol), imine (0.5mmol) and pyridine (2eq. w.r.t. Ir, 2 l) were dissolved in dry toluene (3ml). 7 of these vials were placed in an autoclave, which was closed, purged 3 times with N_2 and 3 times with H_2. The autoclave was pressurized with H_2 to 20-25bar and the reactions were magnetically stirred at room temperature (unless noted otherwise). After the desired time, the autoclave was opened. The solvent in each vial was transferred to a 10ml round bottle and the solvent was removed under vacuum. Degree of conversion and selectivity was determined by ^{1}H NMR ($CDCl_3$). For the e.e. determination the amines were converted to their *N*-acetyl derivatives with 50 l Ac_2O. After filteration on a short silica gel column the filtrate was analysed by HPLC (chiralpak AD or OD column). The absolute configuration was determined by comparing

with commercially available enatiomerically pure products. Racemic samples were prepared by $NaBH_4$ reduction of imines in ethanol as solvent for 30 minutes.

Table 1 HPLC data of N-acetyl derivatives of hydrogenation products [a]

Name	Column	Condition	t (min)	t (min)
Amine **10**(N-acetyl)	OD 250x4.6	Hep/IPA 95/5	t_R=11.573	t_S=14.101
Amine **11**(N-acetyl)	AD 250x4.6	Hep/IPA 95/5	t_1=16.821	t_2=18.955
Amine **12**(N-acetyl)	AD 250x4.6	Hep/IPA 95/5	t_1=14.827	t_2=17.173
Amine **13**(N-acetyl)	AD 250x4.6	Hep/IPA 95/5	t_1=11.403	t_2=13.685
Amine **14**(N-acetyl)	AD 250x4.6	Hep/IPA 95/5	t_1=12.544	t_2=13.803
Amine **15**(N-acetyl)	OD 250x4.6	Hep/IPA 95/5	t_1=10.731	t_2=15.307
Amine **16**(free amine)	Wh01 250x4.6	Hep/EtOH 90/10	t_1=6.603	t_2=8.651
Amine **17**(free amine)	OD 250x4.6	Hep/IPA 90/10	t_1=6.843	t_2=8.122

[a] General conditions for HPLC: flow rate 1.0ml/min, RT, UV 220 nm

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